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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
06/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,206	WANG ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/13/2006 & 12/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

   a. The figure is not properly labeled. As filed, the sheet is identified as "Figure 1," with there being but a single view being presented. In accordance with 37 CFR 1.84(u)(1):

   Where only a single view is used in an application to illustrate the claimed invention, it must not be numbered and the abbreviation "FIG." must not appear.

2. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Specification

3. The disclosure is objected to because of the following informalities:

   a. At page 22, line 25, there appears to be an instance of an unrecognized character being part of the abbreviation for a unit of measure; and

   b. At page 23 there are representations of nucleotide sequences that are not accompanied with the requisite SEQ ID NO.

4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. While there is no *per se* rule requiring applicant to provide an example, much less an example of each and every embodiment encompassed by the claims, applicant is still required to fully enable the entire scope of the claims. Further, narrowing limitations found in the specification cannot be inferred in the claims where the elements not set forth in the claims are linchpin of patentability. *In re Philips Industries v. State Stove & Mfg. Co, Inc..*, 186 USPQ 458 (CA6 1975). While the claims are to be interpreted in light of the specification, it does not follow that limitations from the specification may be read into the claims. On the contrary, claims must be interpreted as broadly as their terms reasonably allow. See *Ex parte Oetiker*, 23 USPQ2d 1641 (BPAI, 1992).

8. In accordance with claim 1, the sole independent claim, one is to "determine the presence, absence and/or amount of the target nucleic acid molecule. As specified in claim 13, the target nucleic acid molecule is selected from the group consisting of "a genomic DNA, a plasmid, a mitochondria DNA, a chloroplast DNA, a messenger RNA, a ribosomal RNA, and a small nuclear RNA." Recognizing that claim, 1 must encompass more than those embodiments set froth in claim 13, claim 1 is construed as also encompassing viral nucleic acids (DNA and RNA).

9. Claims 1-22 have been construed as encompassing the simultaneous detection of an infinite amount of target molecules, including the simultaneous detection of both RNA (mRNA, rRNA, and tRNA, and/or viral RNA) and DNA.

10. The method of claims 1-22 has also been construed as encompassing the detection of mutations (point mutations (insertions and/or deletions), translocations, and inversions).

11. In accordance with claim 19, one is to use either a two-dimensional array, a three-dimensional array, or a four-dimensional array. And in accordance with claim 17, one is to use an array that has from "about 2 to about 1000,000" different probes, and that in accordance with claim 18, the array has an area of from "about 0.01 mm^2 to about 100 cm^2.".

12. A review of the specification finds but a single example, and then but four probes were tethered to the surface of a support via aldehyde group. A review of the specification fails to find where applicant has described the essential starting materials, i.e., 3-dimensional and 4-dimensional, much less arrays that have 100,000 or more probes in a space of but 0.01 mm^2. (Given that claim 17 must further limit claim 1 from which it depends, claim 1 has been construed as encompassing arrays that have more than 100,000 probes on a surface that is either smaller than 0.01 mm^2 or larger than 100 cm^2.)

13. As presently worded, the sample of cells can be lysed by any method. Indeed, applicant at page 7 of the specification states that "any known method" can be sued to lyse the sample of cells. It stands to reason that alkaline lysis of a cell sample will, after prolonged exposure, result in degradation of the nucleic acid present. Further, such a lysis step would also result in degradation of RNA present. Yet, the claimed method is to allow for the detection any and all manner of nucleic acids present, even in a simultaneous manner.

14. Recognizing that RNA is especially sensitive to degradation, be it by chemical treatment and/or as a result of RNases present in the cell, the RNA will typically be degraded unless special steps are taken to protect it. The claimed method specifically requires that no purification of the nucleic acid be conducted. Accordingly, those very compounds, naturally present in the cells, would still be present and are expected to degrade the target(s).

15. As noted above, the method is to result in the quantification of any and all target molecules. The specification, however, is silent as to how one can quantify any molecule. Indeed, as presently worded, the method does not call for the use of any standard. Not having any benchmark by which a skilled artisan would be able to make a comparison, the skilled artisan would be wholly incapable of quantifying anything.

16. The claimed method encompasses detecting point mutations, yet the specification does not set forth a reproducible procedure by which such levels of discrimination could be achieved for a single compound, much less for each of DNA, plasmid DNA, mRNA, tRNA, rRNA, etc.

17. As presently worded, one is to be able to detect a specific sequence found in RNA, yet the same sequence would be present in genomic DNA as the RNA is transcribed from the genomic DNA. The specification fails to teach how one would be able to detect and distinguish the RNA sequence from that of a DNA sequence.

18. The claimed method encompasses the use of a labeled probe that is to hybridize with the nucleic acids in the lysate. The labeled probe may bind not only with the capture sequence of a support, but may also bind, non-specifically, with the support; either of these situations would result in false signals. The claimed method does not recite any method step by which such erroneous signals can be thwarted or compensated for.

19. It is further noted that the method, in accordance with claim 22, requires the use of any of a variety of detectable markers. There is no separation of the incorporated marker from that which has not been incorporated. It stands to reason, therefore, that both will be present when the detection step is performed. Such detection would be wholly erroneous.

20. In accordance with claim 20, the capture probe can be double-stranded DNA. The specification is silent as to how one would be able to detect and/or quantify an infinite number of different nucleic acids when the capture probe is double-stranded, therein not providing a single-stranded region to which the target can hybridize.

21. Prior, as well as post-filing art teaches of numerous problems confronting those of ordinary skill in the art. These problems have not been addressed by the instant disclosure. Absent specific guidance as to how these issues are to be overcome, one of ordinary skill in the art would be forced to trial-and-error experimentation in an effort to overcome these known issues.

Zhang et al., *Bioinformatics*, Vol. 19, No. 1, 2003, page 14, states:

> It is widely recognized that the hybridization process is prone to errors and that the future of DNA sequencing by hybridization is predicated on the ability to successfully cope with such errors. However, the occurrence of hybridization errors results in the computational difficulty of the reconstruction of DNA sequencing by hybridization. The reconstruction problem of DNA sequencing by hybridization with errors is a strongly NP-hard problem. So far the problem has not been solved well.

The claimed method has been construed as encompassing sequencing a nucleic acid via hybridization. Chan (US Patent Application Publication US 2002/0119455 A1):

> [0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the

> maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

The claimed method has been construed as encompassing allele-specific hybridization. Barany et al. (US 2007/0042419 A1), at paragraph 0036 teaches in part:

> For allele-specific oligonucleotide hybridization ("ASO"), the mutation must be known, hybridization and washing conditions must be known, cross-reactivity is difficult to prevent, closely-clustered sites due to interference of overlapping primers cannot undergo multiplex detection, and mutant DNA cannot be detected in less than 5% of background of normal DNA.

Choi et al. (US 2007/0042400 A1), at paragraph 0035, teach:

> [0035] In conventional methods of preparing nucleic acid, polysaccharides such as starch often co-precipitate with nucleic acid. When polysaccharides co-precipitate with nucleic acid, it is difficult to manipulate nucleic acids by amplification methods, such as PCR, or by other detection methods, such as hybridization detection. Polysaccharides may also inhibit digestion with restriction endonucleases and other enzymatic manipulations.

It is noted that the claimed method fairly encompasses the use of genomic DNA, and the use of an enzyme substrate as a label. Yasuno et al., (US 2007/0031829 A1), paragraph 0037, teach in part:

> Certain oligonucleotides hybridize to polynucleotides having complementary sequences. Although DNA hybridization is sequence-specific, it is difficult to completely exclude hybridizations towards very similar nucleotide sequences.

Wang et al., (US 2007/0009954 A1), teach:

> [0004] A number of methods have been developed to score SNPs, including allele-specific hybridization, electrophoretic DNA sequencing, single-nucleotide extension using labeled chain terminators, the "Invader" assay (Third Wave Technologies, Madison Wis.), mass spectrometry, the 5' nuclease assay (Taqman; see below), etc. All of these methods entail assays that are either difficult or expensive to develop, or difficult or expensive to perform.

Rowlen et al., (US 2006/0286570 A1) teach:

> [0004] A variety of methods exist for detection of molecular recognition events. Detection of molecular recognition events such as DNA hybridization, antibody-antigen interactions, and protein-protein interactions becomes increasingly difficult as the number of recognition events to be detected decreases.

22. It is noted that the claimed method places no lower limit on the ability to accurately and reproducibly detect any binding between polymer and unit specific markers.

23. As evidenced above, the art is replete with known issues that directly impact the enablement of the claimed invention. A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.

24. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. Claim 19 is confusing as to what is intended by "a three-dimensional, and a four-dimensional array." The aspect of a three-dimensional array would seemingly be based on three axes x, y, and z, each being at right-angles to one another, which is exemplified by a block of matter. A fourth dimension is at right-angles to each of x, y, z. Time is considered to be the fourth dimension. It is unclear as to how applicant intends the "array" to exist in such a manner or whether applicant had some other structure in mind.

Conclusion

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

29. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

30. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634